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POSITION PAPER

# EAACI Food Allergy and Anaphylaxis Guidelines. Primary prevention of food allergy

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## Abstract

Food allergy can have significant effects on morbidity and quality of life and can be costly in terms of medical visits and treatments. There is therefore considerable interest in generating efficient approaches that may reduce the risk of developing food allergy. This guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Prevention and is part of the *EAACI Guidelines for Food Allergy and Anaphylaxis*. It aims to provide evidence-based recommendations for primary prevention of food allergy. A wide range of antenatal, perinatal, neonatal, and childhood strategies were identified and their effectiveness assessed and synthesized in a systematic review.

Based on this evidence, families can be provided with evidence-based advice about preventing food allergy, particularly for infants at high risk for development of allergic disease. The advice for all mothers includes a normal diet without restrictions during pregnancy and lactation. For all infants, exclusive breastfeeding is recommended for at least first 4–6 months of life. If breastfeeding is insufficient or not possible, infants at high-risk can be recommended a hypoallergenic formula with a documented preventive effect for the first 4 months. There is no need to avoid introducing complementary foods beyond 4 months, and currently, the evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after 4 months once weaning has commenced, irrespective of atopic heredity. There is no evidence to support the use of prebiotics or probiotics for food allergy prevention.

Food allergy can have a significant effect on people's morbidity and quality of life and can be costly in terms of medical visits and treatments. Given the morbidity resulting from food allergy, there is considerable scientific, professional, and lay interest in approaches that may reduce the risk of developing food allergy. This guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Prevention and is part of the *EAACI Guidelines for Food Allergy and Anaphylaxis*. This guideline aims to provide evidence-based recommendations for the primary prevention of food allergy. The primary audience is allergists throughout Europe, but this guideline is also likely to be of relevance to all other healthcare professionals (e.g., doctors, nurses, and pharmacists) in hospitals' primary care and other ambulatory settings.

The causes of food allergy are likely to reflect an interaction between genetic factors and environmental exposure. Genetic factors are currently not modifiable, so strategies to prevent food allergy have tended to focus on early likely exposures to the food proteins most likely to be involved in its pathogenesis. These strategies may be implemented before birth or during breastfeeding, by focusing on the maternal diet, or it may directly target infant nutrition. In addition, there has been a focus on other nutritional factors or supplements that may modify the immune system in a positive direction.

In this guideline, primary prevention of food allergy is defined as prevention of development of food allergy. A wide range of antenatal, perinatal, neonatal, and childhood strategies have been investigated, and the development of the guideline has been informed by a systematic review of interventions for the primary prevention of food allergy in children and adults (1). This systematic review includes only studies with food allergy or food sensitization as outcomes. In instances where there is a lack of clear or consistent evidence, the findings of the literature review have been supplemented with expert consensual opinion. Even though only studies where food allergy or food sensitization was an outcome were included, other possible atopic/allergic symptoms such as atopic dermatitis are also reported. Not all studies reported on confirmed food allergy or sensitization to foods, and some reported food allergy in a combined outcome with other allergies.

## Methods

This guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (2, 3). This is a structured approach to guideline production that is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. We provide below an overview of the approach used.

### Clarifying the scope and purpose of the guideline

This process began in January 2012 with a meeting to discuss the overall approach to guideline development, including detailed discussions on the main aims of the guidelines, the target conditions, clarifying the target populations, to whom the recommendations applied, agreeing the intended end-user group, and ensuring adequate professional and lay representation in the guideline development process.

### Ensuring appropriate stakeholder involvement

Participants represented a range of European countries, and disciplinary and clinical backgrounds (including medical secondary care, primary care, and nursing), and patient groups. The Prevention Task Force continued to work together over the ensuing 18 months through email discussions, teleconferences, and face-to-face meetings.

### Systematic review of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree to one key overarching question (Box 1) that were then pursued through a formal protocol (4) to a systematic review of the evidence (1). Seven bibliographic databases were searched from their inception to September 30, 2012, for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series and cohort studies. Cohort studies were included due to an inability to randomize interventions such as breastfeeding. Excluded were reviews, discussion papers, nonresearch letters and editorials, qualitative studies, case studies, case series, and animal studies.

### Formulating recommendations

We graded the overall strength and consistency of the evidence to translate the key findings from the systematic review into evidence-linked recommendations (5) (Boxes 2 and 3). This involved formulating clear recommendations and making clear the strength of evidence underpinning each recommendation. This ranged from consistent evidence derived from systematic reviews of randomized controlled trials through to evidence derived from expert consensus. Experts identified the implications of implementing the recommendations, barriers and facilitators to the implementation of each recommendation, advice on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation (Table S1).

**Abbreviations**

AGREE II, Appraisal of Guidelines for REsearch & Evaluation; BCG vaccine, bacillus Calmette–Guérin; EAACI, European Academy of Allergy and Clinical Immunology; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IgE, immunoglobulin E; sIgE, specific immunoglobulin E; SPT, skin prick test.

**Box 1:** Key overarching question addressed in the supporting systematic reviews (4)

- What is the effectiveness of approaches for the primary prevention of food allergy?

**Box 2:** Assigning levels of evidence and recommendations (5)

| | |
|---|---|
| Level of evidence | |
| Level I | Systematic reviews, meta-analysis, randomized control trials. |
| Level II | Two groups, nonrandomized studies (e.g., cohort, case–control). |
| Level III | One-group nonrandomized (e.g., before and after, pretest and post-test). |
| Level IV | Descriptive studies that include analysis of outcomes (single-subject design, case series). |
| Level V | Case reports and expert opinion that include narrative literature, reviews, and consensus statements. |
| Grades of recommendation | |
| Grade A | Consistent level I studies. |
| Grade B | Consistent level II or III studies or extrapolations from Level I studies. |
| Grade C | Level IV studies or extrapolations from level II or III studies. |
| Grade D | Level V evidence or troublingly inconsistent or inconclusive studies at any level. |

**Box 3:** Recommendations for primary prevention of food allergy

| | Evidence level | Grade | Key ref |
|---|---|---|---|
| Exclusive breastfeeding is recommended for all infants for the first 4–6 months. | II–III | C | de Silva D, Systematic-Review 2013 (1); Muraro A, 2004, (60) Kull I, 2010 (33); Venter C, 2009 (37); Høst A, 1988 (36), Lucas A, 1990 (30) |
| Dietary restrictions are not recommended for all pregnant or lactating mothers. | I–II | B | de Silva D, Systematic-Review 2013 (1) |
| If breastfeeding is insufficient or not possible: High-risk infants should receive a hypoallergenic formula with documented preventive effect for the first 4 months. Other infants may receive a standard formula. After the age of 4 months, a standard cow's milk-based formula is recommended according to standard nutrition recommendations, irrespective of atopic heredity. | I | A–B | de Silva D, Systematic-Review 2013 (1); Muraro A, 2004 (60) Zeiger RS, 1989, 1992, 1995 (47–49); Odelram H, 1996 (50); Von Berg A, 2003, 2008 (45, 46) |
| Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity. | II–III | C | de Silva D, Systematic-Review 2013 (1) |
| No special dietary restrictions after the age of 4 months for infants with high risk for development of allergic disease No withholding or encouraging exposure to 'highly allergenic' foods such as cow's milk, hen's egg, and peanuts irrespective of atopic heredity, once weaning has commenced. | II–III | C | de Silva D, Systematic-Review 2013 (1) |

### Peer review

A draft of this guideline was externally peer-reviewed by experts from a range of organizations, countries, and professional backgrounds. Additionally, the draft guideline was available on the EAACI Web site for a 2-week period in June 2013 to allow all stakeholders to comment. All feedback was considered by the Prevention Task Force and, where appropriate, final revisions were made according to the feedback received.

### Identification of evidence gaps

The process of developing this guideline has identified a number of evidence gaps (Box 4), and we plan in the future to prioritize the questions that the Prevention Task Force believes should be most urgently addressed.

### Editorial independence and managing conflict of interests

The production of this guideline was funded and supported by EAACI. The funders did not have any influence on the guideline production process, its contents, or the decision to publish. Conflicts of interest statements were completed by all members of the Task Force, and these were taken into account by Task Force chair as recommendations were formulated.

### Updating the guideline

We plan to update this guideline in 2017 unless there are important advances before then.

### Challenges in interpreting the evidence

Food allergy is a complex topic because the symptoms are diverse and allergies can manifest in many different forms. In children, only around one-third of parentally reported food allergy can be confirmed when appropriately investigated. In the population, IgE sensitization to foods, as detected by skin prick test (SPT) or presence of specific IgE (sIgE), is not always associated with clinical reactions and food allergy (6–10). Because the diagnostic accuracy is suboptimal when based solely on history and/or sensitization, if possible a food allergy diagnosis needs to be confirmed by controlled elimination and challenge procedures. Unfortunately, most studies on the prevention of food allergy rely on reported reactions or surrogate markers of food allergy such as sensitization to foods (IgE and/or SPT) and disease outcomes, for example eczema. Moreover, it is important to be aware of the natural course of food allergy, as food allergies develop in the order of exposure to different foods and many children with food allergies, for example cow's milk allergy, develop tolerance during the first years of life. It is therefore important to investigate specific food allergies in the relevant age groups when they experience symptoms suggestive of food allergy and to investigate the specific food allergens that are relevant to that age group and geographic location. Finally, most studies are not sufficiently powered to detect clinically important reductions in the incidence of food allergy.

There are additional ethical and logistical challenges to be considered when interpreting or undertaking food allergy research in young children and infants. For example, it is not ethical to randomize mothers to breastfeeding, and evidence on this topic has therefore been based on high-quality observational studies. However, exclusively breastfed children may not be comparable to others due to self-selection, and these mothers may be more motivated to exclusively breastfeed due to family history of allergic problems or early symptoms in their children. Thus, there is a risk of reverse causation, which is not taken into consideration in most studies.

It is important to note that the quality assessment in the systematic review was, in keeping with standard practice, undertaken on methodological grounds, rather than on the clinical relevance or overall validity of the studies. When extracting the relevant evidence for the guidelines, it is also important to evaluate the scientific quality and clinical relevance of the studies.

Thus, for these recommendations on primary prevention of food allergy, the above-mentioned factors have been considered alongside the formal methodological quality assessment, and experimental studies reporting on confirmed food allergy are ranked highest, whereas studies with self-reported food allergy, atopic symptoms (which may represent food allergy),

**Box 4:** Gaps in the evidence

| | Plan to address | Priority |
|---|---|---|
| The effect of timing of weaning and introduction of different food antigens—while breastfeeding *vs* while not breastfeeding. | Prospective randomized controlled study with sufficient power and well-accepted diagnostic criteria. Probably difficult to address sufficiently, at least in countries with high rate of breastfeeding. | 1 |
| The effect of maternal nutrition and environmental exposures during pregnancy and lactation on development of food allergy in the child. | Prospective randomized controlled study with sufficient power and well-accepted diagnostic criteria. | 2 |
| The preventive effect of different hydrolyzed formulas on food allergy including long-term effects. | Prospective randomized controlled study with sufficient power and well-accepted diagnostic criteria. Europe-wide cohort study looking at the ongoing childhood diet and allergy development (EuroPrevall follow-up, iFAAM). | 3 |
| The effect of prebiotics and probiotics on the incidence and prognosis of food allergy. | Prospective randomized controlled study with sufficient power and well-accepted diagnostic criteria. | 4 |

and sensitization as outcomes were included, but were ascribed less weight. Studies reporting only retrospective data were not included due to their high risk of bias.

### Primary prevention

Almost all of the studies focused on dietary strategies of some type. The studies can be conceptually divided into those which target pregnant women (dietary restrictions and supplements), those which target mothers while breastfeeding (dietary restrictions and supplements), and those which directly target infants (breastfeeding and exclusive breastfeeding, cow's milk formula substitutes, supplements, delaying the introduction of complementary foods, and dietary restrictions). Other preventive initiatives included vaccinations and multifaceted strategies combining dietary and environmental changes or targeting both mothers and infants simultaneously.

Almost all of the studies focused on preventing the development of food allergy from an early age, that is, antenatal and infancy, and many studies focused on infants at high risk of allergic disease (Box 5).

### Antenatal prevention

Overall, there is no evidence to recommend that women modify their diet during pregnancy or take any supplements such as probiotics in order to prevent food allergy in their children (B).

*High-risk families*

Currently, the evidence supporting the role of specific dietary modifications during pregnancy to prevent food allergy in high-risk children is lacking.

A systematic review (11) and two randomized controlled trials (12, 13) found no benefit from restricting common food allergens among pregnant women.

Fish oil supplements may deserve further investigation as two randomized controlled trials suggested trends toward reduced sensitization to egg (14–16).

One trial found that probiotic supplementation during pregnancy among high-risk families reduced allergic sensitization, but there was no evidence specific to food sensitization or food allergy (17).

*Unselected families*

In an unselected population (Box 5), one cohort study indicated that maternal intake of foods rich in n-6 polyunsaturated fatty acids and allergenic foods during late pregnancy may increase the risk of childhood sensitization, as opposed to foods rich in n-3 polyunsaturated fatty acids. Also, high intake of celery and citrus fruits was associated with an increase in food sensitization, but there were no data on food allergy (18).

### Prevention strategies for breastfeeding mothers

There is no evidence to recommend that breastfeeding women should modify their diet or take any supplements such as probiotics in order to prevent food allergy in their children (B).

*High-risk families*

There is no evidence to support intervention strategies for breastfeeding mothers. Two low-quality nonrandomized comparisons found that *maternal dietary changes*, that is, avoidance of the allergenic foods while breastfeeding may not prevent food allergies (19, 20).

**Box 5:** Key terms

| | |
|---|---|
| High risk | In the literature, this is defined as infants/children having at least one parent and/or sibling with a history of allergic disease sometimes also supplemented with an increased cord blood IgE. Here, we have defined high risk as having one or two parents and/or older siblings with a history of allergic disease (food allergy, atopic eczema/dermatitis, asthma, or allergic rhinitis). |
| Unselected | Infants and children in an unselected population including families with and without allergic diseases, that is, low-risk as well as high-risk infants/children. |
| Infancy | In the literature used to describe either first month or first year; here, infancy is defined as the first year of life |
| Children | All age groups of children. |
| Sensitization | A positive skin prick test (SPT) and/or detectable specific IgE (sIgE) irrespective of method or cutoff values and irrespective of clinical reactions. |
| Food allergy | Adverse reaction to a food allergen caused by immunologic mechanisms. |
| Proven food allergy | Food allergy documented by controlled elimination/challenge procedures. |
| Prebiotic | Nondigestible substances that provide a beneficial physiologic effect for the host by selectively stimulating the favorable growth or activity of a limited number of indigenous bacteria. |
| Probiotic | Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. |

One randomized trial found no effect on food sensitization from *probiotic* supplement during late pregnancy and lactation (21, 22).

*Unselected families*
One systematic review (23) and two randomized controlled trials (24, 25) found no differences in most allergy outcomes from fish oil supplements taken by unselected populations of breastfeeding women.

**Prevention strategies during infancy**

*Breastfeeding*
Breastfeeding has many benefits for mother and child and is therefore recommended for all infants. There is a small amount of evidence to support breastfeeding as a means of preventing the development of food allergy (C).

The immunomodulatory components, for example long-chain fatty acid content and oligosaccharides in breast milk, may differ from one mother to another, making it complex to study the effect of breast milk *per se* on allergy prevention (26–28).

*High-risk families*. Although breastfeeding is widely promoted and has many other benefits, there is limited evidence to draw firm conclusions about the benefit for prevention of food allergies in infants at high risk. One systematic review (29) found that most studies identified some benefit of breastfeeding on the risk for food allergy and eczema. One randomized trial of preterm infants indicated a lower risk for cow's milk protein allergy in high-risk infants fed human bank milk as compared to preterm or term formula (30). However, a cohort study found that those who were exclusively breastfed for 5 months or more were more likely to be sensitized to eggs at 1 year, but not at 2 years; no data on food allergy were included (31). Another study found that breastfeeding for 6 months or longer and introducing solid foods after 3 months were associated with an increased risk for atopy, including food sensitization at 5 years (32). However, the latter study was a part of a trial including other interventions, which makes it difficult to evaluate the effect of breastfeeding.

*Unselected families*. The evidence is also mixed in unselected populations. One systematic review (29) and four cohort studies (33–36) found that breastfeeding was associated with a reduced risk of food allergy or sensitization in childhood, three found no association in unselected populations (37–39), but one was not powered for food allergy prevention (37), and another was not targeted at food allergy (39). Furthermore, one cohort study suggested an increased risk for self-reported food allergy in those with high risk only (40).

*Infant formulas as alternatives to breastfeeding*
There is evidence to recommend that hypoallergenic hydrolyzed cow's milk-based formulas with proven clinical preventive efficacy are used for infants at high risk, for the first 4 months, if breastfeeding is insufficient or not possible (B).

*High-risk families*. There is significant evidence regarding the benefits of hydrolyzed cow's milk formulas for infants. Two systematic reviews (29, 41) and five randomized trials (42–49) suggested that *extensively hydrolyzed whey or casein formulas* might have a protective effect. Although one of those (i.e., the GINI study) was not designed for evaluation of food allergy, it reported on atopic eczema/dermatitis and allergic manifestations including gastrointestinal food allergy (food allergy with manifestations in the gastrointestinal tract), and food sensitization (45, 46). Two other randomized comparisons failed to find a benefit (50, 51). However, in one of these, the children were breastfed for a long period and the formula was introduced after the age of 6 months (50), which may indicate that the window of opportunity for prevention with hydrolyzed formulas is likely to be restricted to the first 6 months. Another randomized trial combining extensively hydrolyzed casein-based formula with avoidance of some foods for varying periods and maternal diet also found a benefit of extensively hydrolyzed casein-based formula on food allergy until 3 years of life (47–49), but is difficult to identify the effect seen to the hydrolyzed formula only. In one of the systematic reviews, food allergy was not reported separately, only as part of atopic symptoms (41). The Swedish study (50) reported on symptoms suggestive of food allergy, whereas others reported on confirmed food allergy.

*Partially hydrolyzed infant formula* may also have a protective effect. Two systematic reviews (52, 53), two randomized controlled trials (45, 54), and two nonrandomized comparisons (55, 56) found that partially hydrolyzed formula may protect against food allergy, and the latter two found that 'food allergy symptoms' or 'sensitization' may be reduced when compared to standard cow's milk formula. As described above, the GINI study (45) reported on eczema and allergic manifestations, including gastrointestinal food allergy, rather than food allergy (45, 46). One randomized trial (57) and one nonrandomized comparison (58) failed to find any benefit. However, in one (57), outcomes were only assessed by telephone interview.

A few studies have compared the possible preventive effects of extensively and partially hydrolyzed formulas. They indicate that the preventive efficacy is dependent on the specific formula studied. The degree of hydrolysis alone may not correlate with the efficacy of prevention of food allergy (59), and also different extensively hydrolyzed formulas may have different effects. Thus, an extensively hydrolyzed whey formula used in the GINI study (45) was not effective for prevention, whereas another extensively hydrolyzed whey formula was effective in other studies (42, 43) and extensively hydrolyzed casein formula has been effective in several studies (42, 43, 47, 48, 60). A few studies indicated that some extensively hydrolyzed formulas (based on casein or whey) might have a better preventive effect as compared to partially hydrolyzed whey formula (42) or a blend of casein and whey (44), although a meta-analysis found no significant difference (53).

There was no evidence to support the use of soy-based formulas in allergy prevention. One systematic review (61) and two randomized trials (57, 62) found that soy-based formulas

might not protect against food allergies when compared to cow's milk formula or to other alternatives. However, in one of the latter (57), outcomes were assessed by telephone interview.

*Unselected families*. There were no available data, as these studies have not been performed.

### Dietary supplements

There is no evidence to recommend prebiotics or probiotics (Box 5) or other dietary supplements based on particular nutrients to prevent food allergy (B).

*Pre- and probiotic supplements*

*High-risk families*. Probiotic supplements have been tested during infancy, but there is little evidence to support their effectiveness. Four randomized controlled trials (63–66) found no benefit against food allergy or sensitization.

*Unselected families*. There is no evidence to support prebiotics or probiotics to prevent food allergy in unselected or mixed-risk populations. One systematic review (67) found insufficient evidence about the benefits of prebiotics in infant formulas, and one randomized trial using a particular blend of neutral oligosaccharides and pectin-derived acidic oligosaccharides (68) found benefit for eczema, but not for food sensitization. Two systematic reviews (69, 70) and one randomized trial (71) found no benefit of using probiotics in unselected or mixed populations.

However, different microorganisms have been used in different studies, and it appears that different microbial strains may have different effects, which may explain the inconsistent results as regards a possible preventive effect of specific strains of probiotics.

*Other supplements*

One randomized trial (72) found no evidence to recommend or avoid cow's milk-based human milk fortifiers in premature infants, although the study may not be powered for food allergy as an outcome. One cohort study (73) found no evidence to recommend or avoid vitamins A and D in water-soluble form or in peanut oil.

### Introduction of complementary foods

There is insufficient evidence to make specific recommendations about the timing of the introduction of complementary foods and individual solid foods as regards food allergy prevention for all children (C). However, a few studies indicate that it might be an advantage not to introduce solids before 4 months of age (C). In addition, other aspects have to be considered, such as the infant's developmental readiness, parental opinion/needs, the nutritional needs, and the risk for developing very selective eating habits. Therefore, we recommend introducing complementary foods from 4 to 6 months of age according to standard local practices and the needs of the infant, irrespective of atopic heredity.

*High-risk families*

Another strategy has been to delay the introduction of solid foods. Infants may not need or may not be developmentally ready to start eating solid foods until sometime within the age range of 4–6 months, so this period is often considered as an appropriate minimum weaning age. Some studies suggest that introducing solid foods earlier than 4 months may increase the risk of food sensitization and eczema in infants with a family history of allergy. However, delaying the introduction of solid foods beyond 4 months does not seem to confer any additional protective benefits. Two low-quality cohort studies (74, 75) found no evidence that introducing solid foods after 4 months in high-risk infants prevented food allergy. This finding is supported by the low prevalence of food allergy in randomized trials on hydrolyzed formulas without delaying introduction of solid foods after 4–6 months (42, 43).

*Unselected families*

One systematic review (76) and two cohort studies (77, 78) found that introducing solid foods after 4 months did not protect against food allergy, but one of these (77) found that introduction of solid foods before 4 months increased the risk of later allergy. Two cohort studies found reduced food sensitization when solids were introduced earlier than 4 months (37, 79), in the latter only in those at high risk.

*Introduction of potential food allergens*

The timing of potential food allergen introduction may be important, but there is insufficient rigorous scientific evidence in this regard; the present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods during infancy (B-C). Therefore, for primary prevention, we recommend no withholding or encouraging of exposure to 'highly allergenic' foods such as cow's milk, hen's egg, and peanuts irrespective of atopic heredity, once weaning has commenced.

Two randomized controlled trials (80–82) found that there was no increased risk of food allergy from early exposure to cow's milk protein in the first 3 days of life, but in one (80, 81), the diagnostic criteria for food allergy were weak and not documented by challenges, while for the other one (82), the symptoms were nonspecific and food allergy was not reported. Another randomized trial (83) and one cohort study (36) suggested an increased risk of confirmed cow's milk allergy if children in unselected populations were fed cow's milk protein in the first few days.

There is little additional evidence about avoiding potential food allergens. One cohort study found (84) that consuming fish regularly during the first year of life may protect against food allergy or sensitization.

In a large cross-sectional study, not included in the systematic review because of its design, comparing Israeli and UK Jewish children, the prevalence of peanut allergy was 10-fold higher in the UK than in Israel, whereas the median monthly consumption of peanuts in Israeli infants was very high but merely absent in the UK (85). This observation

reports an interesting association, which awaits confirmation in further studies (86). Another cross-sectional study with retrospective data on introduction indicated that introduction of egg between 4 and 6 months might protect against egg allergy (87), but due to the methods, these data need to be confirmed in other studies.

One recent nested control study, including children from a prospective birth cohort study, found that children diagnosed with food allergy by 2 years were introduced solids earlier (≤16 weeks) and were less likely to be receiving breast milk when cow's milk protein was first introduced into their diet (88). Thus, introducing potential food allergens while continuing to breastfeed may provide a reduced risk for development of food allergy. However, studies using rigorous design methodologies are required to answer this important question with greater certainty.

*Combining dietary with environmental modifications*

Although the quality of evidence is low, there is some evidence from six studies (89–95) to suggest that combining dietary with different environmental recommendations or modifications, such as reduction in exposure to house dust mite allergens, during infancy for high-risk families may be useful (B). Further research in this area would be helpful because there are few data about specific food allergy outcomes, and it is difficult to differentiate cause-and-effect relationships in the available literature.

### Prevention strategies during childhood and adulthood

Very little has been published about strategies to prevent food allergy targeting children and adults, and all available studies are in unselected populations. One systematic review (96) found that bacillus Calmette–Guérin (BCG) vaccinations had no protective effect against food allergy, and another systematic review (97) found no protective benefit from fish oil supplements. A cohort study (98) found that taking vitamins before age five may protect against food allergy, but the quality of evidence is very low (C).

## Conclusions and future perspectives

Based on this evidence, families can be provided with some practical advice about preventing food allergy, particularly among infants at high risk due to parent and/or older siblings with allergic disease (Box 6). The advice for all mothers includes the consumption of a normal healthy diet without restrictions during pregnancy and lactation. For all infants, exclusive breastfeeding is recommended for the first 4–6 months of life. If breastfeeding is insufficient or not possible for the first 4 months, infants at high risk can be recommended a hypoallergenic formula with documented preventive effect for the first 4 months of life. There is no need to avoid introducing complementary foods beyond 4 months or for infants and children to take supplements such as prebiotics or probiotics. In addition, the present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after the age of 4 months, once weaning has commenced, irrespective of atopic heredity.

**Box 6:** Summary of recommendations for primary prevention of food allergy

Recommendations for all infants:

- No special diet during pregnancy or for the lactating mother.
- Exclusively breastfeeding for 4–6 months.

Further recommendations for high-risk infants:

- If supplement is needed during the first 4 months, a documented hypoallergenic formula is recommended.

Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity.

Although no cost-effect or cost-benefit analysis has been published, the above recommendations are easy to follow and of low cost and are not detrimental (D). It may be necessary to consider the levels of evidence, as well as the price and the possibility for reimbursement of extra expenses for the different hydrolyzed formulas.

While considering these recommendations, it should be remembered that a lack of evidence for some issues does not necessarily mean they are not useful, merely that there is yet insufficient proof of a potential benefit. In this regard, there is a need for future studies.

## Expert Panel

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## Author contributions

Antonella Muraro, Chair of the EAACI Food Allergy and Anaphylaxis Guidelines Initiative, has steered and coordinated the publication. Susanne Halken chaired the guidelines

group with support from Arne Høst. Debra de Silva and Sukhmeet Panesar undertook the supporting systematic reviews under the supervision of Aziz Sheikh. All authors participated in the discussion of the systematic review, the evidence table, recommendations, gaps, and specific sections and approved the final version.

## Conflicts of interest

Susanne Halken has provided scientific advice for ALK-Abelló. Antonella Muraro has provided scientific advice for Meda. Tony DuBois has provided scientific advice for ALK-Abelló and received funding from ALK-Abelló to support his research activities. Philippe Eigenmann has provided scientific advice for Danone, Novartis, ALK-Abelló, DBV technologies and Stallergenes; he has received funding for research activities from LETI, Nestlé, and ThermoFisher. Arne Høst has provided scientific advice for ALK-Abelló and Danone. Carina Venter has produced educational material for Danone, Mead Johnson, and Nestlé and has received research funding from Thermofischer, Danone, and Mead Johnson. Debra de Silva, Sukhmeet Panesar, and Aziz Sheikh have received funding for coordinating guideline production and generating the systematic reviews from EAACI. Aziz Sheikh has provided scientific advice to ALK-Abelló, Meda, Lincoln Medical, ThermoFisher, Pfizer, and Stallergenes; he is on the Anaphylaxis Campaign UK's Scientific Committee, World Allergy Organization's Anaphylaxis Special Committee, UK Resuscitation Council's Anaphylaxis Committee, and the BSACI's Standard of Care Committee. Gideon Lack has no conflict of interests. Kirsten Beyer has received funding for research activities from the European Union, German Research Foundation, Berliner Sparkasse, BEA-Stiftung, Food Allergy and Anaphylaxis Network, Food Allergy Initiative, Danone, ThermoFisher, DST Diagnostics, Allergopharma and has received honoraria or consultation feed from Danone, MedaPharma, ALK-Abelló, Novartis, Unilever, Allergopharma, MedUpDate, ThermoFisher, HAL. Graham Roberts and Hasan Arshad have provided scientific advice for Danone. Kate Grimshaw has provided scientific advice for Danone. Valérie Verhasselt has received research funding from Nestlé. Liam O'Mahony is a scientific consultant to Alimentary Health Ltd and has received research funding from GSK. George du Toit has received lecture fees from Nutricia and indirectly from the many sponsors of the KCL Allergy Academy. Cesmi A Akdis has received research grants from Allergopharma, Stallergenes, Actellion, and Novartis. Besides, Cesmi A Akdis was President (2011–2013), Past President (2013–2015), and ExCom member in EAACI, which has received financial support from several relevant business entities.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Barriers and facilitators to implementation, audit criteria, and resource implications of recommendations.

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